PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number: WO 94/01136
A61K 47/36	A1	(43) International Publication Date: 20 January 1994 (20.01.94)

(21) International Application Number: PCT/DK93/00227

(22) International Filing Date: 6 July 1993 (06.07.93)

(30) Priority data:
0895/92 7 July 1992 (07.07.92) DK

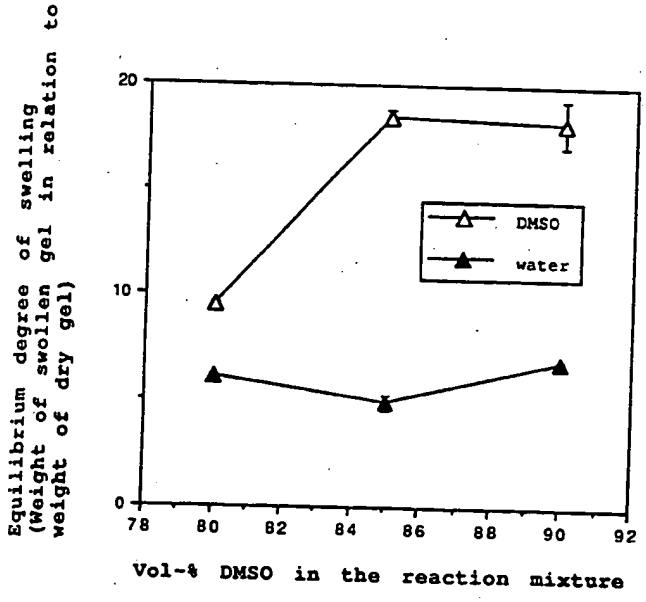
(71)(72) Applicants and Inventors: BRØNDSTED, Helle [DK/DK]; HOVGAARD, Lars [DK/DK]; Paltholmterrasserne 83F, DK-3520 Farum (DK).

(74) Agent: HOFMAN-BANG & BOUTARD A/S; Adelgade 15, DK-1304 Copenhagen K (DK).

(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: A DRUG DELIVERY DEVICE AND A METHOD OF MAKING SUCH DEVICE



(57) Abstract

A drug delivery device comprising a polymer matrix and a drug contained in or surrounded by the matrix which polymer matrix is a cross-linked hydrogel matrix comprising a dextranase degradable polymer and a cross-linking agent providing covalent bonded network linkage between the polymer chains. The device is suitable for delivering drug to the colon. A method of making the device comprising: (a) dissolving a dextranase degradable polymer in a solvent; (b) adding a cross linking agent capable of cross-linking the polymer with covalent bonds to the solution; (c) allowing the cross-linking agent to react with the dextranase degradable polymer to provide a cross-linked hydrogel matrix, and loading the drug into said solution before or after the reaction between the polymer and the cross-linking agent has finished.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**FR**	France	**MR**	Mauritania
AU	Australia	**GA**	Gabon	**MW**	Malawi
BB	Barbados	**GB**	United Kingdom	**NE**	Niger
BE	Belgium	**GN**	Guinea	**NL**	Netherlands
BF	Burkina Faso	**GR**	Greece	**NO**	Norway
BG	Bulgaria	**HU**	Hungary	**NZ**	New Zealand
BJ	Benin	**IE**	Ireland	**PL**	Poland
BR	Brazil	**IT**	Italy	**PT**	Portugal
BY	Belarus	**JP**	Japan	**RO**	Romania
CA	Canada	**KP**	Democratic People's Republic of Korea	**RU**	Russian Federation
CF	Central African Republic			**SD**	Sudan
CG	Congo	**KR**	Republic of Korea	**SE**	Sweden
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovak Republic
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LU**	Luxembourg	**TD**	Chad
CS	Czechoslovakia	**LV**	Latvia	**TG**	Togo
CZ	Czech Republic	**MC**	Monaco	**UA**	Ukraine
DE	Germany	**MG**	Madagascar	**US**	United States of America
DK	Denmark	**ML**	Mali	**UZ**	Uzbekistan
ES	Spain	**MN**	Mongolia	**VN**	Viet Nam
FI	Finland				

A drug delivery device and a method of making such device

The present invention relates to drug delivery devices for delivering drugs to the colon and comprising a polymer matrix and a drug contained in or surrounded by the matrix.

A large number of drugs are very sensitive to proteolytic enzymes contained in the digestive juices of the stomach and the small intestine. Drugs, such as peptides and proteins, are degraded by the proteolytic enzymes, thus reducing the absorption substantially.

Though oral administration is much more convenient and acceptable to the patient, the most common mode of delivering drugs, such as peptides and proteins, is by parental administration.

Investigations have shown that the concentration of proteolytic enzymes in the colon juices is much lower than the concentration in the juices of the stomach and the small intestine.

It would therefore be very advantageous to find a suitable technique for delivering drugs selectively to the colon by administration through the alimentary canal.

Polymeric materials such as hydrogels have been widely used in drug carrier systems for controlled release or used as stimuli sensitive devices. Such devices are for instance described in "Hydrogels in Medicine and Pharmacy", N.A. Peppas (Ed.), CRC Press, 1987. The formulations described therein are generally not biodegradable. The release of pharmacologically active agents "loaded" into such gels is typically controlled by simple diffusion in the device which depends on the water content in

the gel. These gels are therefore not suitable for drug delivery to specific regions of the intestines after oral administration.

EP Patent Application 357 401 discloses a biodegradable hydrogel matrix comprising a protein, a polysaccharide, and a cross-linking agent. However, this composition is not used for oral administration.

US Patent 4 024 073 discloses a hydrogel composition comprising a water-soluble polymer containing a chelating agent bound to the polymer chain, and a polyvalent metal ion cross-linking the polymer molecules through the chelating agent. The hydrogel is useful as a carrier for timed release of drugs and medicaments and is not targeted to the colon.

JP Patents 1 156 912, JP 62 010 012, JP 5 721 315, DE Publication 3 400 106 and US Patent 4 496 553 describe the preparation of compressed tablets for slow-release of drugs using soluble polymers or polysaccharides. These are all conventional tablets disintegrating in a time-dependent fashion and are not specifically targeted to the colon.

Patent Application GB 2 066 070 describes a pharmaceutical formulation of a tablet for release of an active substance in the colon. This tablet contains the active component in the centre covered by a coating consisting of cellulose and derivatives thereof. The coating is degradable by bacteria present in the colon. A drawback of this system is, however, that the coating can dissolve in the stomach or the upper gastro-intestinal tract. Therefore, the patent describes a system which is vulnerable to inter-individual variations in intestinal transit time and which does not specifically release the active substance in the colon.

Osmotic drug devices for delivering a drug to the colon is described in GB Patent Applications 2 166 051 and 2 166 052. These devices comprise a laminated membrane surrounding a compartment containing a drug. The membrane results in a time delay in the commencement of substantial release of the drug. Such osmotic drug devices have the same disadvantages as the device described in GB Patent Application 2 066 070.

A publication relating to the field of the present invention is "Chemically-modified polysaccharides for enzymatically-controlled oral drug delivery" (Kost et al., Biomaterials, 11, 695-698, 1990). This paper describes a system of ionically cross-linked starch used for controlled release of macromolecules to the intestines. The system takes advantage of the presence of amylases in the small intestine and does therefore not target the release to the large intestine or the colon.

Recently, Rubinstein et al. (Pharm. Res., 9, 276-278, 1992) have described colonic drug delivery by use of a chondroitin matrix. The system consists of a drug embedded in a compressed matrix of chondroitin. This matrix may disintegrate at any time during the transit of the small intestine. Thus, this system is not suitable for site-specific drug delivery to the colon.

WO Publication 92/00732 describes a composition for oral delivery of therapeutically active substances to the colon. The composition comprises a matrix core having the active substance or substances dispersed therein, and an outer cover layer without any active substance. Both the matrix core and the outer cover layer are based upon polysaccharides such as pectin and/or dextran forming coacervate through polyvalent cation cross-linking where the cation is bi- or trivalent.

In the stomach of a patient having a normal gastric acid function, hydrogen ions will penetrate into both the outer layer and the core of the composition and by ion-exchange substitute hydrogen ions for the polyvalent cations, leaving the polysaccharide chains non-complexed to a great extent and more or less holding the composition together by sterical effects rather than by cation connections.

This means that the composition is more or less disintegrated during passage through the stomach and the small intestine, and that the disintegration during this passage is extremely dependent on the presence of other cations, residence time of the composition and particularly on the gastric acid function of the very patient. In other words, a composition of the above type may be able to deliver active substances to the colon of a patient, if the composition is specifically composed for the patient. Such composition is therefore not commercially suitable.

The use of hydrogels containing biodegradable bonds has previously been described by Brøndsted and Kopecek in Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 18, 345-346, 1991. The hydrogels exhibit pH-dependent swelling due to incorporated acidic groups in the polymer backbone and biodegradability due to enzymatically labile cross-links. The system utilizes the presence of microbial azoreductases in the colon. The hydrogels disintegrate after the degradation of cross-links and the release of polymer backbone.

By using these acidic hydrogels it is possible to avoid any substantial degradation and release of drug in the stomach. However, the degradation of the hydrogel and thus the release of drug to the colon appears to be very slow, and when passing the colon only a part of the drug

may be released.

Drug delivery to the colon has been obtained by using dextran prodrugs (Larsen et al., Pharm. Res., 6, 995-999, 1989) which release the active substance after cleavage by microbial enzymes being present only in the colon. The drug was covalently bound to the dextran. As the prodrug reached the colon, bacterial dextranases were able to break down the dextran releasing the drug after hydrolysis of the covalent bond. A disadvantage of this system consists in a severe drug loading problem. Furthermore, the drug must possess a suitable functional group for modification and be able to withstand experimental conditions for coupling to the dextran carrier.

It is therefore evident that there is a need for an oral drug delivery device with improved selectivity to the colon.

The object of the present invention is to provide such oral drug delivery device for delivering drug to the colon by use of which device it is possible to deliver one or more drugs to the colon without substantial loss of drug in the stomach, the small intestine, and faeces.

The drug delivery device according to the invention comprises a polymer matrix and a drug contained in or surrounded by the matrix and is characterized in that the polymer matrix is a covalent cross-linked hydrogel matrix comprising dextranase degradable polymer and a cross-linking agent providing network linkage between the polymer chains.

As mentioned before, dextranases are only present in the colon. In the drug delivery device according to the invention the drug is protected by the cross-linked dextra-

nase degradable polymer when the device passes through the stomach and the small intestine. When reaching the colon, the polymer matrix is degraded by dextranase and the drug is released.

The rate of degradation of the polymer matrix and thereby the release of drug depends on several factors such as the choice of dextranase degradable polymer, the cross-linking agent, the degree of cross-linking, the water content of the hydrogel matrix and the configuration and size of the finished device. The device according to the invention can be constructed so that practically all of the drug is released in the colon.

The dextranase degradable polymer in the device according to the invention must be essentially resistent to the digestive juices of the stomach and the small intestine.

Preferably, the dextranase degradable polymer is dextran or a modified dextran. Several methods for modifying dextran is known. See for instance W.M. Meckernan and C.R. Ricketts, Biochem J., 76, 117-120, 1960 regarding preparation of diethylaminoethyldextran, and K.Nagasawa et al., Carbohydr. Res., 21, 420-426, 1972 regarding synthesis of dextran sulphate.

By using modified dextran instead of ordinary dextran it is possible to obtain a hydrogel matrix with a more hydrophobic or a more hydrophilic as well as charged character. This can be used to control the swelling properties of the hydrogel matrix. The dextranase degradable polymer is also chosen depending on which drug is to be loaded into the hydrogel matrix, so that the dextranase degradable polymer will not react with the drug in a manner which irreversibly inactivates the drug.

Particularly preferred is sulfated, alcoxylated, oxydated or esterificated dextran.

The dextranase degradable polymer may have a molecular weight between 10,000 and 2,000,000 g/mol, preferably between 40,000 and 2,000,000 g/mol.

If the dextranase degradable polymer is dextran, a molecular weight between 70,000 and 500,000 is optimal.

The cross-linking agent can be any non-toxic agent which is able to provide a network linkage of the polymer structure. The polymer may be held together by covalent bonds, such as urethane, ester, ether, amide, carbonate, or carbamate bonds. Diisocyanate that provides urthane bonds, such as hexamethylenediisocyanate and 1,4-phenylenediisocyanate, are preferred as cross-linking agent.

The degree of cross-linking in the hydrogel, like the composition of the hydrogel itself, affects the degradation kinetics, loading, and the overall release profile of the matrix. That is, a higher degree of cross-linking will generally result in slower degradation and release, while a lower degree of cross-linking will result in faster degradation and release.

Of course, the influence which the degree of cross-linking has on the release of the drug depends upon the molecular size of the drug and the way the drug is loaded into the device. Preferably, the cross-linking agent constitutes 0.05-25 mol-% of monomeric units in the hydrogel.

The drug can in principle be any type of drug. The device according to the invention is especially advantageous for use when administering drugs for treatment of diseases in

the colon, e.g. steroids, 5-aminosalicylic acid, anti-inflammatory agents, anti-cancer agents, enzymatic agent, and bacterial cultures, or for administration of drugs which are unstable in the stomach and/or the small intestine, e.g. peptides such as insulin, vasopressin, or growth hormones, proteins, enzymes, and vaccines.

The device according to the invention is also advantageous for use in time-delayed administration of drugs.

By use of the device according to the invention drugs, such as agents for treatment of rheumatism and other analgesic agents, can be administered to the patient at bedtime and be effective in the morning, as the time it takes the device to reach the colon is about 8 hours.

The drug can be loaded into the hydrogel matrix in several ways. For instance the drug, or a gelatine capsule containing the drug, can be coated by the hydrogel matrix, or the drug can be contained in the lumen of the hydrogel device, i.e. the drug is surrounded by a thicker layer of hydrogel matrix.

Methods of incorporating drug in hydrogels are common knowledge to a person skilled in the art and are for example described in S.W. Kim et al., Pharm. Res., 9, 283-290, 1992.

In a preferred embodiment of the device according to the invention, the drug is homogeneously dispersed in the cross-linked hydrogel matrix.

Depending on how the drug is loaded, the hydrogel matrices can be formed into capsules, tablets, films, microspheres, or the like. The compositions formulated using the hydrogel matrices can include conventional pharmaceutical carriers or excipients, adjuvants, etc.

The device according to the invention can contain more than one drug, e.g. the device can contain one drug of high molecular weight in the lumen of the hydrogel matrix and another drug of lower molecular weight dispersed homogeneously in the matrix.

It will be obvious to a skilled person that other combinations also comprising drugs which are released in the stomach or the small intestine are possible.

Another object of the invention is to provide a method of making a drug delivery device according to the invention.

The method according to the invention comprises

a) dissolving a dextranase degradable polymer in a solvent,

b) adding a cross-linking agent capable of cross-linking the polymer with covalent bonds to the solution,

c) allowing the cross-linking agent to react with the dextranase degradable polymer to provide a cross-linked hydrogel matrix.

The drug can be loaded into the device before the cross-linking reaction has finished by use of several methods. These methods are also common knowledge to persons skilled in the art and are for instance described in S.Z. Song et al., J. Pharm. Sci., 70, 216-219, 1981.

In a preferred embodiment the drug is loaded into the device after the cross-linking reaction has finished by means of the following steps:

a) the hydrogel matrix is predried, preferably to a water content lower than 30 weight-% and particularly

lower than 10 weight-%,

b) the dried hydrogel matrix is brought into contact with a liquid drug or a drug solution and is allowed to swell,

c) If desired, the hydrogel is dried.

This last method provides a very simple and easy method of making a device according to the invention by which the drug is homogeneously dispersed.

To describe the invention further a series of examples are given.

Fig. 1 is a graph showing the equilibrium degree of swelling of a device according to the invention depending on the contents of DMSO.

Fig. 2 is a graph showing the equilibrium degree of swelling of a device according to the invention depending on the contents of cross-linking agents.

Fig. 3 is a graph showing the equilibrium degree of swelling of a device according to the invention depending on the molecular weight of dextran.

Fig. 4 is a graph showing the degradation in the cecum and in the stomach, respectively, of a device according to the invention depending on time.

Fig. 5 shows the release profiles of hydrocortisone from a device according to the invention.

EXAMPLE 1

Preparation of biodegradable dextran hydrogels

1.5 grams (9.25 mmol glucose units) of dextran 70 (MW 70,000, commercially available from Pharmacia) was dissolved in 8.5 ml (85 vol-%) anhydrous dimethylsulphoxide (DMSO). Immediately upon dissolution of the dextran to a clear slightly viscous solution 86 µl (0.46 mmol ~5 mol-%) of hexamethylenediisocyanate (HDI, cross-linking agent) was added. This was done in a thoroughly dried glass bowel, as the cross-linking reaction is obstructed by traces of water. The solution was transferred to the reaction mould for fabrication of films by means of a needle and syringe. The mould consists of two water-jacketed teflon-coated aluminum blocks, between which blocks the solution was placed. By controlling the distance between the blocks using a spacer ring, it is possible to control the thickness of the resulting hydrogel film. The temperature was set to 70 °C. The cross-linking reaction took place at this temperature for 24 hours.

In a similar manner four other hydrogels containing dextran 70 and various amounts of HDI and DMSO were synthesized. Two gels had 2.5 and 10 mol-% of HDI and two had 80 and 90 vol-% of DMSO.

Also the molecular weight of dextran was varied. Hydrogels were made with dextran 10, 500 and 2000 (MW 10,000, 500,000 and 2,000,000, respectively).

Table 1 shows a scheme of the synthesized hydrogels.

TABLE 1

Sample	Dextran (Molecular weight)	DMSO (Vol-%)	HDI (Mol-%)
A	70 000	85	2.5
B	70 000	85	5
C	70 000	85	10
D	70 000	80	10
E	70 000	90	10
F	500 000	85	5
G	2 000 000	85	5

The vol-% is calculated in relation to the volume of the resulting reaction mixture. The mol-% is calculated on the basis of the molar content of glucose in the amount of dextran used.

EXAMPLE 2

Determination of equilibrium degree of swelling of biodegradable dextran hydrogels

The equilibrium degree of swelling of hydrogels prepared as in example 1, samples A-G, was studied. Three discs were cut from each hydrogel and the weight of the swollen gel in water and DMSO was measured. The gels were washed with water and dried at room temperature for 2 days and in vacuum at 40-50 °C for 2 days. The equilibrium degree of swelling was evaluated as the ratio of the mass of swollen gel to that of the dry gel.

Figure 1 illustrates the dependence of equilibrium degree of swelling of hydrogels containing various amounts of

DMSO in the reaction mixture. An increasing amount of DMSO in the reaction mixture results in an increase of the equilibrium degree of swelling of the resulting hydrogel. This is more distinct in DMSO than in water.

Figure 2 shows that the equilibrium degree of swelling decreases as the cross-linking density of the hydrogel increases.

From Figure 3 it can be seen that if the molecular weight of the dextran is varied, it does not have any substantial influence on the equilibrium degree of swelling.

The equilibrium degree of swelling is greater in DMSO than in water. Thus, DMSO appears to be a good example of a possible medium for drug loading into the hydrogels.

EXAMPLE 3

Evaluation of degradability of hydrogels in-vitro

The in-vitro degradability of hydrogels was investigated using dextranase (50 kilo Dextranase Units/g). Discs, 5 mm in diameter and 1.6 mm in thickness, of hydrogel films prepared as described in example 1, were cut and swollen to equilibrium in 0.1 M acetate buffer pH 5.4. After swelling equilibrium was reached, the discs were transferred to the enzyme mixture consisting of 1 ml 0.1 M acetate buffer pH 5.4 and 0.5, 3 or 12 µl dextranase. The mixture was incubated in a water bath at 37 °C, and the time required for complete dissolution of the discs, τ, was recorded. Degradation of the gels was followed by a decrease in thickness.

Table 2 shows τ for different gels when the enzyme mixture consisted of 12 µl dextranase/ml buffer. As cross-linking density increases, τ increases, and thus the

degradability decreases. This also relates to the equilibrium degree of swelling; the higher the degree of swelling, the higher the degradability of the hydrogel. However, the results also indicate that structural factors, too, influence on the degradability of the hydrogels.

Table 3 shows that as the amount of dextranase increases, the rate of degradation increases.

TABLE 2

Sample	τ (min)
A	18 ± 1.5
B	36 ± 4.6
C	60 ± 4.9
D	255 ±15
E	46 ± 1
F	46 ± 2
G	33 ± 0.6

TABLE 3

Sample	Amount of dextranase (µl)	τ (min)
B	0.5	157 ± 5.3
B	3	131 ±14.8
B	12	36 ± 4.6

EXAMPLE 4

Evaluation of degradability of hydrogels in-vivo

The dry weight of 6 samples B hydrogel discs 5 mm in diameter was recorded and the discs pre-swollen in isotonic potassium phosphate buffer pH 7.4. Each disc was placed in a gauze bag. The gauze bags were implanted in the stomach and the cecum of male SD rats (200-300 g) and secured to the intestinal wall to prevent excretion of the gels. The rats were then allowed water and food ad libitum. At various times (1, 2 and 3 days) the rats were sacrificed and the gels recovered. The gels were washed in DMSO and water and then dried. The dry weight was recorded and the degradation of the gels was evaluated as % degradation (loss in dry weight in percent of initial dry weight). The initial dry weight was between 42 and 45 mg.

Figure 4 shows that after 3 days the gels implanted in cecum were degraded, whereas gels implanted in the stomach did not degrade. This shows that degradation of the gels takes place in-vivo and that this takes place in the cecum and not in the stomach.

EXAMPLE 5

Loading and in-vitro release of hydrocortisone

Hydrogel discs, prepared as described in example 1, 5 mm in diameter and 1.6 mm in thickness (sample B), were washed in water and dried. After drying, the discs were immersed in a drug solution of hydrocortisone in DMSO (72.5 mg/ml). After 24 hours the gels were dried in vacuum af 50 °C for 2 days. Release of hydrocortisone from the discs was studied in 0.1 M acetate buffer pH 5.4 with (24 µl dextranase/ml buffer) and without dextranase present. A gel was immersed in 5 ml release medium and

kept in a water bath at 37 °C. At time intervals of eight minutes when enzymes were present and thirty minutes when no enzymes were present, samples of 2.5 ml were taken and replaced by fresh medium. The amount of released hydrocortisone was determined by reverse phase HPLC on a C-18 column with methanol:water 60:40 as mobile phase, UV detection at 242 nm and an injection volume of 20 µl.

After 30 min 0.72 mg of hydrocortisone was released from the gel immersed in enzyme-containing buffer as compared with 0.11 mg from the gel in pure buffer. This shows that the release is drastically increased in the presence of dextranases.

Figure 5 shows the release profiles of hydrocortisone from the hydrogels. A much quicker release of hydrocortisone is obtained when dextranase is present in the release medium.

Patent Claims

1. A drug delivery device comprising a polymer matrix and a drug contained in or surrounded by the matrix, characterized in that the polymer matrix is a cross-linked hydrogel matrix comprising a dextranase degradable polymer and cross-linking agent providing covalent bonded net-work linkage between the polymer chains.

2. A drug delivery device according to claim 1, characterized in that the dextranase degradable polymer is dextran.

3. A drug delivery device according to claim 2, characterized in that the dextran is sulfated, alcoxylated, oxydated or esterificated.

4. A drug delivery device according to claims 1-3, characterized in that the dextrane degradable polymer has a molecular weight between 10,000 and 2,000,000 g/mol, preferably between 40,000 and 2,000,000 g/mol, and especially between 70,000 and 500,000 g/mol.

5. A drug delivery device according to claims 1-4, characterized in that the cross-linking agent is an urethane bond-forming agent.

6. A drug delivery device according to claim 5, characterized in that the urethane bond-forming agent is hexamethylenediisocyanate or 1,4-phenylenediisocyanate.

7. A drug delivery device according to claims 1-6, characterized in that the cross-linking agent constitutes 0.05-25 mol-% of monomeric units in the

hydrogel.

8. A drug delivery device according to claims 1-7, c h a r a c t e r i z e d in that the drug is homogeneously dispersed in the hydrogel matrix.

9. A drug delivery device according to claims 1-7, c h a r a c t e r i z e d in that the drug is surrounded by the matrix.

10. A method of making a drug device according to claims 1-9, c h a r a c t e r i z e d in that the method comprises

a) dissolving a dextranase degradable polymer in a solvent,

b) adding a cross-linking agent capable of cross-linking the polymer with covalent bonds to the solution,

c) allowing the cross-linking agent to react with the dextranase degradable polymer to provide a cross-linked hydrogel matrix, and loading the drug into said solution before or after the reaction between the polymer and the cross-linking agent has finished.

11. A method according to claim 10, c h a r a c t e r i z e d in that the drug is surrounded by the polymer and the cross-linking agent before the cross-linking reaction has finished, whereafter the cross-linking reaction is allowed to finish.

12. A method according to claim 10, c h a r a c t e r i z e d in that the drug solution or in liquid form is loaded into the cross-linked hydrogel by allowing the predried hydrogel to absorb the drug.

Figure 1

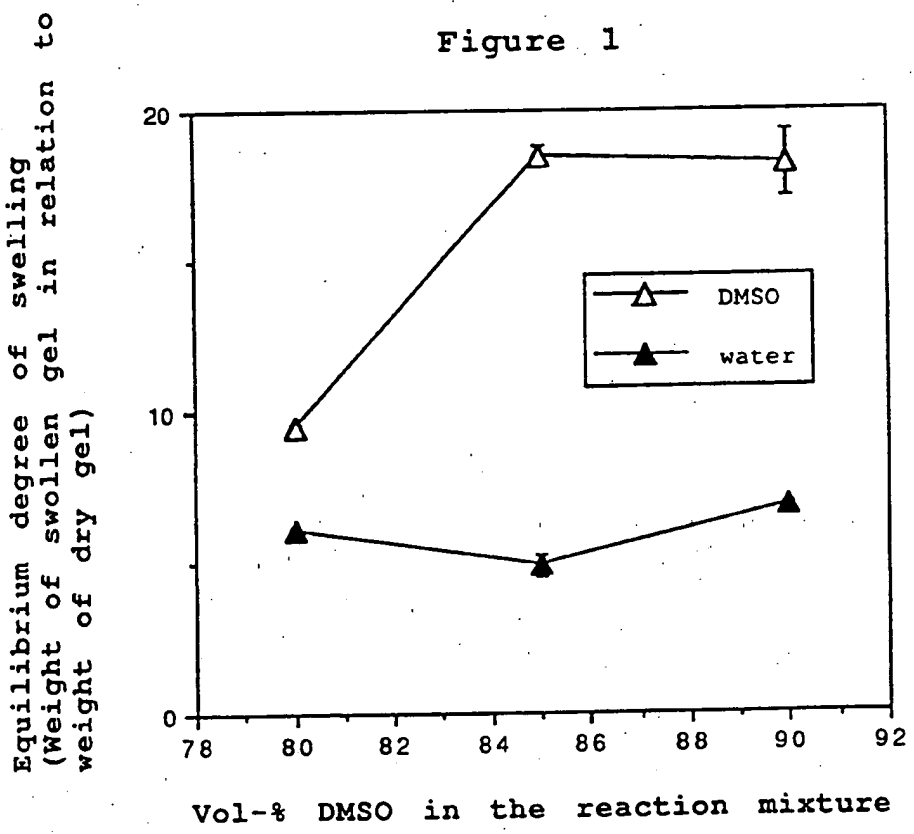

Equilibrium degree of swelling
(Weight of swollen gel in relation to
weight of dry gel)
20
10
0
78
80
82
84
86
88
90
92
DMSO
water
Vol-% DMSO in the reaction mixture

Figure 2

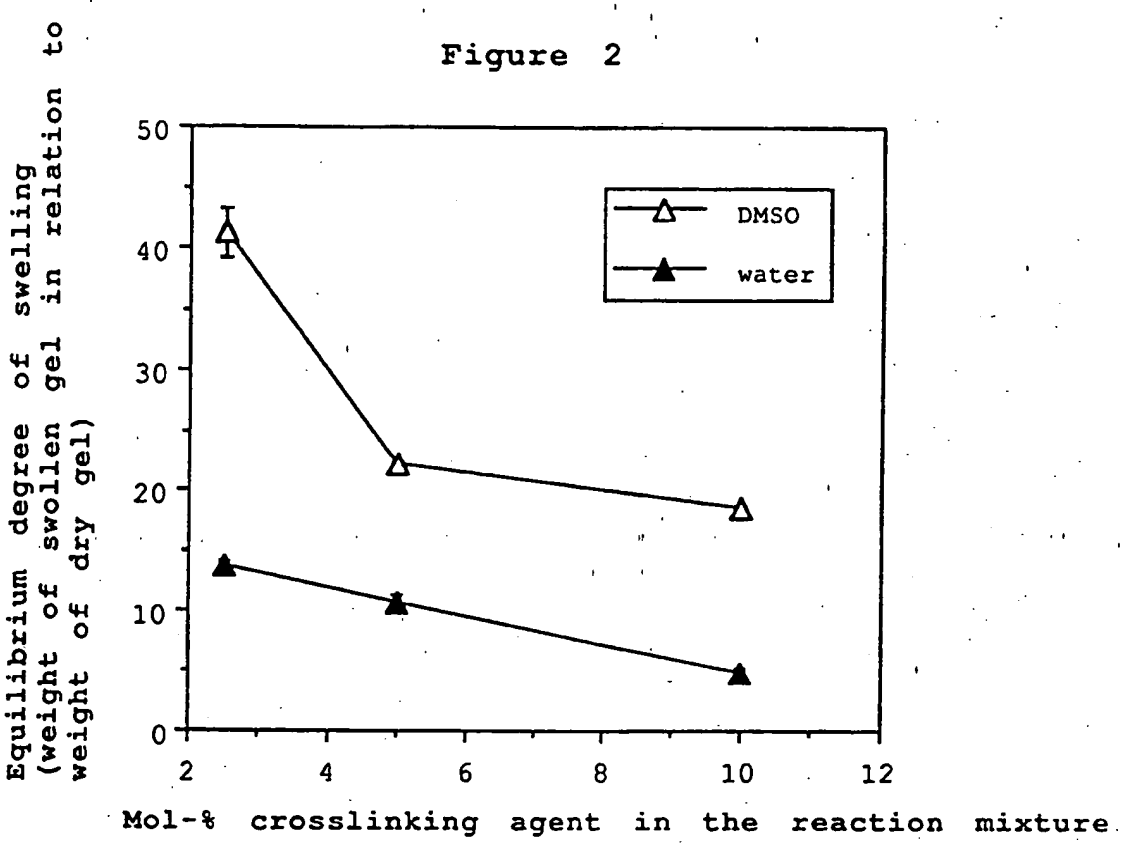

Equilibrium degree of swelling
(weight of swollen gel in relation to
weight of dry gel)
50
40
30
20
10
0
2
4
6
8
10
12
DMSO
water
Mol-% crosslinking agent in the reaction mixture

Figure 3

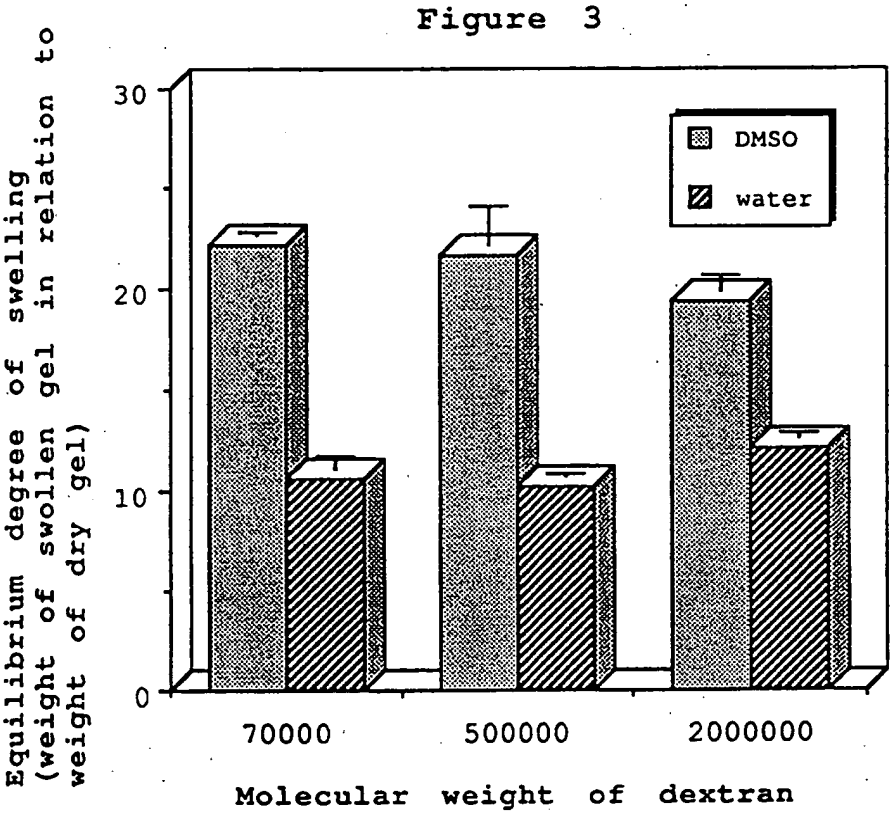

Equilibrium degree of swelling
(weight of swollen gel in relation to
weight of dry gel)
30
20
10
0
DMSO
water
70000
500000
2000000
Molecular weight of dextran

Figure 4

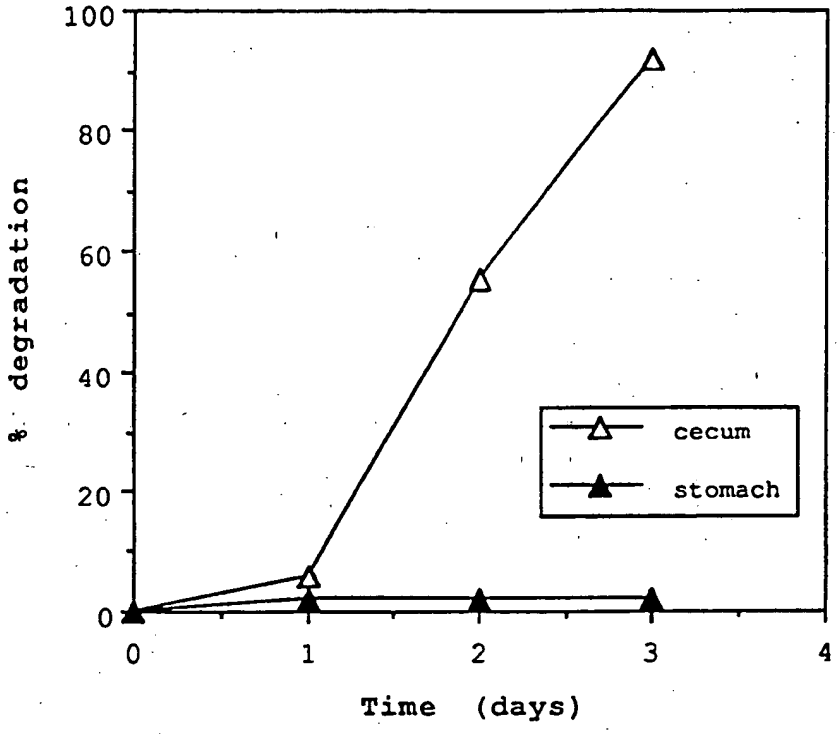
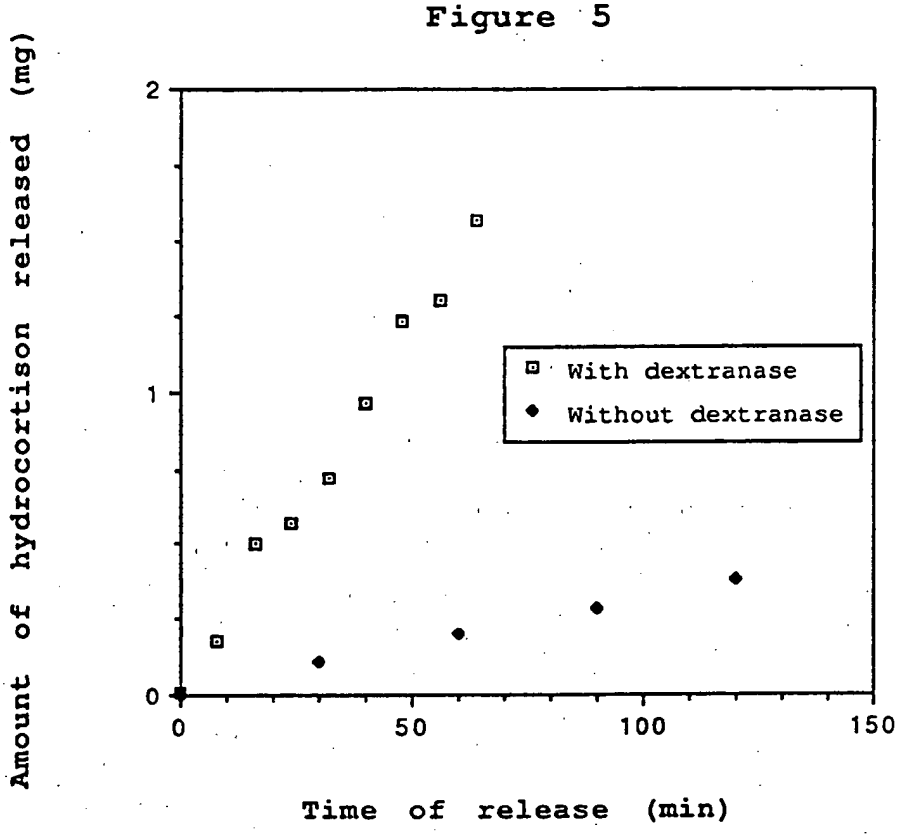


Figure 5


Amount of hydrocortison released (mg)
2
1
0
0
50
100
150
With dextranase
Without dextranase
Time of release (min)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 93/00227

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 47/36
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, BIOSIS, WPI, CLAIMS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, A, 9200732 (KABI PHARMACIA AB ET AL), 23 January 1992 (23.01.92) --	1-12
X	US, A, 4024073 (H SHIMIZU ET AL), 17 May 1977 (17.05.77) --	1-12
X	GB, A, 2078110 (CRINOS INDUSTRIA FARMACOBIOLOGICA S.P.A.), 6 January 1982 (06.01.82) --	1-12

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 October 1993	18 -10- 1993
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Jonny Brun Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

26/08/93

International application No.
PCT/DK 93/00227

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 9200732	23/01/92	AU-A- 8227291	04/02/92
		SE-A- 9002339	05/01/92
US-A- 4024073	17/05/77	GB-A- 1388580	26/03/75
		JP-C- 983023	22/01/80
		JP-A- 48074549	08/10/73
		JP-B- 54016979	26/06/79
GB-A- 2078110	06/01/82	AT-B- 390882	10/07/90
		AU-A- 7165181	24/12/81
		BE-A- 889146	01/10/81
		CA-A- 1148861	28/06/83
		CH-A,B- 650156	15/07/85
		DE-A,C- 3123823	22/04/82
		FR-A,B- 2484838	24/12/81
		JP-C- 1713456	27/11/92
		JP-B- 3071403	13/11/91
		JP-A- 57031607	20/02/82
		NL-A- 8102675	18/01/82
		SE-B,C- 449816	25/05/87
		SE-A- 8103833	21/12/81
		US-A- 4371518	01/02/83